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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/088,632	07/30/2002	Erik D'Hondt	B45201	7231

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EXAMINER	
MOSHER, MARY	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,632	D'HONDT ET AL.	
	Examiner	Art Unit	
	Mary E. Mosher, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-35,41-44 and 46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-35,41-44 and 46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Objections

The objection to the claim numbering is withdrawn. Applicants state that the claims were amended and renumbered during the International stage, and upon entry into the U.S. National stage, claims 1-25 were pending, not claims 1-26. A number of errors must have occurred in preparing this application for the U.S. national stage, because no copy of any international stage amendment was included in the record. Since the most recent response includes a complete copy of the pending claims, the examiner will henceforth use the same claim numbering as in the response.

Priority

Applicants have kindly provided a certified copy of the GB priority document, and state that a certified copy was timely filed with the International Bureau.

Claim Rejections - 35 USC § 112

The rejection of claim 32 (now 31) for new matter is withdrawn in view of the claim amendment.

Claim Rejections - 35 USC § 103

The rejections of claims under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Couch et al (Journal of Infectious Diseases 176:S38-S44, 1997), Chaloupka et al (European Journal of Clinical Microbiology & Infectious Disease 15:121-127, 1996), and Kistner et al (WO 00/15251) are withdrawn, in view of applicant's GB priority document which predates Kistner et al.

New Claim Rejections - 35 USC § 112

On reconsideration, the statement that claims 30, 31, and 36 are drawn to allowable subject matter, is withdrawn because of new grounds of rejection.

Claims 26-35, 41-44, and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is confusing because the preamble says that the composition is monovalent, but the claim also recites "no more than 15 ug per combined dose of vaccine." How can the vaccine be simultaneously monovalent and combined? This affects the dependent claims. Furthermore, claims 26 and 41 recite "a suitable adjuvant", but do not indicate what the adjuvant must be suitable for. For example, an adjuvant suitable for vaccinating chickens or pigs is not the same as a suitable adjuvant for vaccinating humans. All three species are of current concern in the art as hosts for a possible pandemic strain of influenza.

Claims 26-35, 41-44, and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There are several aspects to this "written description" rejection.

First, all of the claims require "antigen from an influenza virus that is associated with a pandemic outbreak, or has the potential to be associated with a pandemic outbreak." This involves a genus of influenza virus antigens, the genus involving

pandemic or potentially pandemic influenza virus strains. By definition, a pandemic strain differs from the influenza viruses that were in circulation when the application was filed, containing "a new haemagglutinin compared to that of the currently circulating strains" (see definitions on pages 1-2 of the specification). Since one skilled in the art is unable to predict what strains of influenza virus will arise in the future, or to predict which strains will rapidly spread worldwide, clearly there are many unpredictable species within this genus. The specification provides some guidance as to some characteristics that might be found in a future pandemic strain (page 2, lines 9-25), but this guidance is not sufficient to reasonably convey that applicants possessed the required genus of pandemic viruses. There is no working example involving a vaccine against a pandemic strain. Therefore, it is concluded that the specification does not reasonably convey possession of the genus of pandemic virus antigen, which is required for all of the claims.

Second, claims 26, 27, 32-35, 41-44, and 46 require a generic "suitable adjuvant." The term "adjuvant" encompasses a wide variety of materials. Although the claims do not explicitly state that the composition is suitable for humans, the specification makes no mention of vaccinating animals, and is concerned throughout with human vaccines. If "suitable" is taken as meaning "suitable for humans", the prior art indicates a great deal of unpredictability in the application of adjuvant influenza virus vaccines in humans, see for example Deliyannis et al (Vaccine 16:2058-2068, 1998), page 2066. The specification contains working examples using only aluminum salts. Considering the unpredictability in the art, and the single species of adjuvant shown in

the working example, it is concluded that the specification does not reasonably convey possession of the full genus of "suitable adjuvants" for a low-dose vaccine in humans.

New Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 26, 32, 33, 34, 41, 42, 44, and 46 are rejected under 35 U.S.C. 102(a) as being anticipated by Rimmelzwaan et al (Vaccine 17:1355-1358, March 17, 1999). Rimmelzwaan teaches that avian influenza virus A (H5N1) has the potential to be associated with a pandemic outbreak, see the first paragraph of the publication. Rimmelzwaan teaches a monovalent vaccine with 10 ug of purified glycoprotein per dose in combination with a Quillaja glucoside adjuvant, see page 1356, sections 2.1 and 2.2. This clearly meets each and every limitation of these claims.

New Claim Rejections - 35 USC § 103

Claims 26, 27, 32, 33, 34, 41-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Couch et al (Journal of Infectious Diseases 176:S38-S44, 1997), Chaloupka et al (European Journal of Clinical Microbiology & Infectious Disease 15:121-127, 1996), and De Donato et al (Vaccine 17:3094-3131, August 6, 1999). As discussed in the previous Office action, Couch explicitly suggests developing adjuvants to produce satisfactory immune responses with lower doses of antigen to decrease the burden of vaccine production in a pandemic

circumstance. Chaloupka teaches that current human influenza vaccines are required to contain 15 ug hemagglutinin per strain per dose, indicating that Couch suggests a vaccine with less than 15 ug hemagglutinin per dose. De Donato teaches an adjuvant that is safe and effective in increasing the immune response to influenza vaccine in humans. Unlike the early study mentioned in Couch, De Donato teaches at least a 4-fold enhancement in antibody response in many of the participants. See table 2. Therefore, it would have been within the ordinary skill of the art to use the adjuvant taught by De Donato to carry out the suggestion of Couch, with reasonable expectation of success. Although the publications do not discuss in detail egg-derived vaccines, whole-virus vaccines or the degree of purity of subunit vaccines, these are conventional variations in the influenza vaccine art. The publications do not state in detail the amount of hemagglutinin to include in a lowered-dose vaccine, this is seen as a matter of routine optimization. Therefore, the invention as a whole is prima facie obvious, absent unexpected results.

Claims 44 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Couch, Chaloupka, and De Donato as applied to claims 26, 27, 32, 33, 34, 41-43 above, and further in view of Riberdy et al (Journal of Virology 73:1453-1459, 1999). As discussed in the previous Office action, these claims differ from the above in that they specify H2 or H5 hemagglutinin. Riberdy teaches that H5N1 virus is thought to have pandemic potential, and is being used to develop a vaccine intended for humans, see page 1453, column 1. Therefore, it would have been obvious

to choose an H5N1 virus for use to vaccinate against a potential pandemic strain. The invention as a whole is therefore prima facie obvious, absent unexpected results.

Prior art

Claims 28-31 are free of the prior art, because the prior art generally teaches away from using aluminum salt adjuvants in influenza vaccines. Claim 35 is free of the prior art for reasons of record.

The following publications are cited as of interest.

Deliyannis et al (Vaccine 16:2058-2068, 1998) teaches adjuvanted influenza vaccines which appear effective at low dose in mice, but teaches that those in the influenza art do not believe that mouse studies are predictive of human responses. Deliyannis points out that the adjuvanted vaccines, if effective in humans, would be useful "when antigen from a newly arisen strain is in short supply."

Kistner et al (Vaccine 16: 960-968, 1998) teaches a low-dose vaccine compositions containing aluminum hydroxide adjuvant, see Figure 5 and page 962. However Kistner teaches that Vero cell-derived antigen is several-fold more potent than egg-derived antigen. Therefore Kistner does not provide motivation to use egg-derived antigen in low-dose vaccines.

Davenport et al (Journal of Immunology 100:1139-1140, 1968) teaches away from using aluminum salt adjuvants in human influenza vaccines, because no enhancement of immunogenicity was observed in human studies. There is no reason to

believe that Davenport anticipates the invention, because Davenport administered 300-400 CCA units per dose[1].

Palache et al (Vaccine 11:892-908, 1993) teaches that influenza vaccines with 10 ug or 15 mg hemagglutinin produce similar results in immunocompetant populations.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary E. Mosher, Ph.D. whose telephone number is now 571-272-0906. The examiner can normally be reached on M-T and alternate F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can now be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is still 703-872-9306.

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[1] While there does not appear to be a standard conversion between CCA units and ug hemagglutinin, Brandon et al (Journal of Immunology 98:800-805, 1967, cited in Davenport) indicates that the vaccines used in Davenport had at least as much hemagglutinin per unit CCA compared to whole virus vaccine, and Montagne et al (Reviews of Infectious Diseases 5:723-727, 1978) provides evidence that several typical whole virus vaccines of 300-400 CCA units/dose had >40 micrograms of hemagglutinin/dose, see table 2. Therefore, there is reason to believe that the adjuvanted vaccine of Davenport exceeded hemagglutinin limitation stated in the claims.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is still 703-308-0196.

2/10/04
~~1/22/04~~

MARY E. MOSHER
PRIMARY EXAMINER
GROUP ~~1800~~ 1600